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Experimental Manipulation of Pituitary Hemorrhage Induced by Intraperitoneal Injection of a Hypertonic Solution in Mice

Chie Iga, Ichiro Koshimizu, Sumio Takahashi and Yasuo Kobayashi*

Department of Biology, Faculty of Science, Okayama University, Okayama 700, Japan

ABSTRACT—Acute and intense hemorrhage into the anterior pituitary in mice can be induced by the intraperitoneal injection of a 35% glucose solution at a dose of 0.03 ml/g bw. Experimental manipulations that stimulate or inhibit this pituitary hemorrhage were investigated. A rise in plasma osmolality paralleled a rise in the incidence of pituitary bleeding. Water deprivation facilitated the incidence of pituitary hemorrhage at a low dose of a 35% glucose solution (0.015 ml/g bw) that was without effect in control mice. In contrast, the incidence of the pituitary hemorrhage reduced in nursing dams. Enhancement of the pituitary hemorrhage was obtained by the pretreatment with agents including norepinephrine, epinephrine, bromocriptine and thiamazole despite a low dose of a glucose solution applied. On the other hand, pituitary hemorrhage was evidently suppressed by treatment with agents including haloperidol, sulpiride, metoclopramide, pentobarbital and ether inhalation prior to the injection of a high dose of the glucose solution. These results suggested a stimulative effect of dopamine on induction of the pituitary hemorrhage.

INTRODUCTION

Our previous study has revealed that intraperitoneal injection of either 9% NaCl, 8% $NaHCO_3$, 3 M glucose or 3 M sucrose caused acute and intense hemorrhage into the anterior pituitary in mice [13]. Ultrastructural evidence at the initial stage of this pituitary hemorrhage was "diapedesis" by which red blood cells migrate through the wall of capillaries without structural destruction of endothelial cells [12]. Intense hemorrhage eventually resulted in profound necrosis of the anterior pituitary followed by some restoration in volume afterwards [15].

No causal analysis has been available, at present, on this pituitary hemorrhage. Then, the present study was designed to explore some experimental conditions and pharmacological agents that act as either stimulative or inhibitory ones on the experimental pituitary hemorrhage.

MATERIALS AND METHODS

Animals

Young and old male mice, and lactating dams of the Jcl/ICR strain were used. Animals were injected intraperitoneally (ip) with a 35% glucose solution at a dose indicated below, and they were killed by decapitation 30 min after the injection. Pituitary hemorrhage was inspected with the naked eyes by dark red color and edematous appearance of the anterior pituitary.

Physiological studies

Animals were divided into 5 groups. In Group 1, mice were used to test the effective dose of a 35% glucose solution. Animals were injected ip with the solution at a dose of either 0.015 ml/g bw, 0.02ml/g bw or 0.03 ml/g bw, respectively. Group 2 consisted of young and old mice at 5, 20 and 30 weeks of age, and they received the ip injection of 35% glucose at a low dose of 0.02 ml/g bw. In Group 3, mice were subjected to water deprivation for 1 or 3 days, and they were given a 35% glucose solution at a low dose of 0.015 ml/g bw. In Group 4, nursing dams of postpartum day 17 were used, and they received a 35% glucose solution at a dose of 0.03 ml/g bw. Day-matched lactating dams were served as the control and their pups were separated for 24 hr prior to the ip injection of a 35% glucose solution. In Group 5, the hematocrit (%) was determined and the plasma osmolality (mOsm/kg) was measured with a Shimadzu OSM-1 Osmometer in mice injected ip with a 35% glucose solution at either a low dose of 0.02 ml/g bw or a high dose of 0.03 ml/g bw.

Pharmacological analysis

The following agents were administered subcutaneously (sc) at the back skin of the neck either alone or in combination 30 min prior to the ip injection of a 35% glucose solution. Animals were divided into 2 groups; Group 1 was applied for an excitatory experiment and Group 2 for a suppressive one.

Animals in Group 1 were given an insufficient low dose of a 35% glucose solution (0.02 ml/g bw). Test agents used and each dose were as follows; phenylephrine-HCl 1 μg/g bw, an α-adrenaline receptor agonist; isoproterenol-HCl 1 μg/g bw, a β-adrenaline receptor agonist; phenoxybenzamine-HCl 20 μg/g bw, an α-adrenaline receptor antagonist; dl-propranolol-HCl 1 μg/g bw, a β-adrenaline receptor antagonist; adrenocorticotropic hormone (ACTH) 40 mU/g bw; vasopressin 5 mU/g bw; 5-hydroxytryptophan (5-HTP) 25 μg/g bw for 3 days; 5-hydroxytryptamine (5-HT) 2 μg/g bw; norepinephrine 3 μg/g bw, epinephrine 2 μg/g bw; bromocriptine methylate 5 μg/g bw, a D-2 dopamine receptor agonist; thiamazol 100 μg/g bw, an anti-thyroid agent.

In Group 2, suppression of this pituitary hemorrhage was tested in mice pretreated with following agents either alone or in combination; d-chlorpheniramine maleate 50 μg/g bw, a histamine receptor antagonist; dl-p-chlorophenylalanine either 100 μg/g bw or 100 μg/g bw for 3 consecutive days, a serotonin synthesis inhibitor; haloperidol

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* To whom requests for reprints should be addressed.

either 5 μg/g bw or 5 μg/g bw for consecutive 3 days, a dopamine receptor antagonist metochlopropamide-HCl 30 μg/g bw, a D-2 dopamine receptor antagonist; sulpiride 150 μg/g bw, a D-2 dopamine receptor antagonist; ether vapor inhalation for 20 min; pentobarbital sodium 50 μg/g bw; and adrenaline receptor agonists and antagonist with the same doses used in Group 1. Statistical significance was assessed by Student's t-test for the mean of hematocrit and osmolality and by χ^2-test for the incidence of pituitary hemorrhage.

RESULTS

Histology

Intense hemorrhage into the anterior pituitary occurred after the ip injection of a 35% glucose solution at a dose of 0.03 ml/g bw. The anterior pituitary was somewhat edematous with the blood cells and plasma migrated out of the capillaries, and the distended hypophysial lumen contained a large mass of blood cells (Fig. 1).

FIG. 1. A parasagittal section of the mouse pituitary gland after intraperitoneal injection of a 35% glucose solution. Erythrocytes migrated from sinusoidal capillaries are darkly stained in the anterior pituitary. The hypophysial lumen is distended and filled with a large mass of blood cells (arrow). Bar indicates 0.2 mm.

Physiological analysis

Intraperitoneal injection of a 35% glucose solution at a dose of 0.03 ml/g bw resulted in pituitary hemorrhage in all 55 young mice tested (100%), but a low dose of either 0.02 ml/g bw or 0.015 ml/g bw was not efficacious (Table 1).

Aging increased an incidence of this pituitary hemorrhage in 8 out of 13 mice (61.5%) at 20 weeks of age and in 9 out of 11 mice (81.8%) at 30 weeks of age despite the low dose (0.02 ml/g bw) of a glucose solution administered (Table 2).

TABLE 1. Effect of intraperitoneal injections of 35% glucose on the incidence of pituitary hemorrhage in 5-week-old male mice

Dose of 35% glucose (ml/g bw)	No. of mice hemorrhaged /no. of animals tested (%)
0.015	0/12 (0%)
0.02	0/27 (0%)
0.03	55/55 (100%)

Animals were sacrificed 30 min after the injection.

TABLE 2. Age-related incidence of anterior pituitary hemorrhage in mice given the intraperitoneal injection of 35% glucose at a low dose of 0.02 ml/g bw

Age (weeks)	No. of mice hemorrhaged /no. of mice tested (%)
5	0/27 (0)
20	8/13 (61.5)*
30	9/11 (81.8)*

* $p<0.01$ vs 5 weeks.
No significant difference between those of 20 and 30 weeks.

TABLE 3. Effect of water deprivation on the incidence of anterior pituitary hemorrhage in mice given the intraperitoneal injection of 35% glucose solution at a low dose of 0.015 ml/g bw

Water deprivation (day)	No. of mice hemorrhaged /no. of mice tested (%)
0	0/12 (0%)
1	6/12 (50%)*
3	12/12 (100%)*++

*, $p<0.01$ vs day 0; +, $p<0.01$ vs day 1.

Water deprivation for 1 and 3 days increased an incidence of this pituitary hemorrhage in 6 out of 12 mice (50%) and in 12 of 12 mice (100%), respectively, despite the lowest dose (0.015 ml/g bw) of a glucose solution administered (Table 3).

In contrast, in nursing dams of day 17 postpartum an injection of a high dose (0.03 ml/g bw) of 35% glucose resulted in the bleeding only 4 out of 10 (40%), whereas in day-matched control dams, whose pups were separated for 24 hr prior to the glucose treatment, the injection of 35% glucose resulted in pituitary bleeding in 6 of 6 dams (100%) (Table 4).

TABLE 4. Effect of lactation on the incidence of pituitary hemorrhage and the hematocrit values (HCT) in suckling mice on day 17 postpartum

	No. of hemorrhage /no. of mice tested (%)	HCT (%)
Control	6/6 (100)	54.4±1.4
Suckling	4/10 (40)*	55.2±0.4 NS

In the control, pups were removed their mother for 24 hr before the ip injection of 35% glucose at a dose of 0.03 ml/g. *, $p<0.05$ vs control; NS, non-significant.

High levels of hematocrit values were observed after a 35% glucose treatment, but no significant difference was obtained between two groups of a non-bleeding low dose (0.02 ml/g bw) and a heavy-bleeding high dose (0.03 ml/g bw) (Table 5). Serum osmolality in a low dose and high dose groups was significantly higher than that in the normal control ($p<0.01$, in both comparison, Table 5).

Table 5. Hematocrit (%) and osmolality (mOsm/kg) of mice 30 min after the intraperitoneal injection of a 35% glucose solution at either a low dose of 0.02 ml/g bw or a high dose of 0.03 ml/g bw

	Dose of a 35% glucose solution		
	Control	0.02 ml/g bw	0.03 ml/g bw
Hematocrit	47.3±1.0 (8)	57.1±0.6 (9)[1)]	58.0±0.8 (9)[2)]
Osmolality	301.8±2.0 (8)	360.9±3.6 (9)[3)]	397.1±3.7 (9)[4)]

Number of animals is in parentheses. 1), 2), 3) and 4) are different from each control value ($p<0.01$). No significant difference between 1 and 2, and significant difference between 3 and 4 ($p<0.01$).

Enhancement of pituitary hemorrhage

Pituitary hemorrhage was induced by a low dose of 0.02 ml/g bw (a sub-threshold dose) of a 35% glucose solution in combination with pretreatment of following drugs. The results indicated that bleeding occurred in 8 out of 10 mice (80%) with norepinephrine, in 5 out of 7 mice (71.4%) with epinephrine, and in 16 out of 20 mice (80%) with bromocriptine, and in 9 out of 10 mice (90%) with thiamazole, respectively (Table 6). No effects were observed with injections of adrenocorticotropin, vasopressin, serotonin and serotonin precursor.

Table 6. Enhancement of pituitary hemorrhage by agents given subcutaneously prior to the intraperitoneal injection of 35% glucose at a low dose of 0.02 ml/g bw

Agents	Dose (μg/g)	No. of mice hemorrhaged /no. of mice tested (%)
Control	—	0/27 (0)
Phenylephrine	1	0/8 (0)
Isoproterenol	1	0/6 (0)
Phenoxybenzamine	20	0/8 (0)
Propranolol	1	0/6 (0)
Adrenocorticotropin	40 mU	1/10 (10)
Vasopressin	5 mU	0/10 (0)
5-Hydroxytryptophan	25×3 days	0/7 (0)
5-Hydroxytrypatamine	2	1/10 (10)
Norepinephrine	3	8/10 (80)*
Epinephrine	2	5/7 (71.4)*
Bromocriptine	5	16/20 (80)*
Thiamazole	100	9/10 (90)*

* $p<0.01$ vs control

Suppression of pituitary hemorrhage

Pituitary hemorrhage was suppressed by the sc treatment of following drugs prior to the ip injection of a 35% glucose solution at a high dose of 0.03 ml/g bw. In this experiment, the rate of suppression was 0 out of 55 mice in the control (0%) (Table 7). Then, pituitary hemorrhage was suppressed in 8 out of 17 mice (47.1%) with ether inhalation, in 16 out of 20 mice (80%) with pentobarbital, in 3 out of 14 mice (21.4%) with haloperidol, in 5 out of 23 mice (21.7%) with sulpiride, in 4 out of 21 mice (19.0%) with a single dose of metoclopramide and, further, in 10 out of 16 mice (62.5%) with metoclopramide for consecutive 3 days (Table 7).

Table 7. Suppression of pituitary hemorrhage by agents given subcutaneously prior to the intraperitoneal injection of 35% glucose at a high dose of 0.03 ml/g bw

Agents	Dose (μg/g bw)	No. of mice suppressed /no. of mice tested (%)
Control	—	0/55 (0)[1)]
Phenylephrine	1	0/6 (0)
Isoproterenol	1	0/6 (0)
Phenoxybenzamine	20	0/6 (0)
Propranolol	1	0/8 (0)
Chlorpheniramine maleate	50	0/8 (0)
p-Chlorophenylalanine	100	0/6 (0)
p-Chlorophenylalanine	100×3 days	0/6 (0)
Haloperidol	5×3 days	3/14 (21.4)*
Sulpiride	150	5/23 (21.7)*
Ether vapor	20 min	8/17 (47.1)*
Pentobarbital	50	16/20 (80.0)*
Metoclopramide	30	0/13 (0)
Metoclopramide	60	4/21 (19.0)*
Metoclopramide	30×3 days	10/16 (62.5)*
Ether vapor +Metoclopramide	(20 min) 30×3 days	16/20 (80.0)*
Pentobarbital +Metoclopramide	50 30×3 days	39/39 (100)[2)]*
Pentobarbital +Metoclopramide	50 60	11/11 (100)*

*, $p<0.01$ vs control. Hematocrit of 1) and 2) was 51.7±0.5 and 50.5±0.5, respectively.

Further, metoclopramide (30 μg/g bw) for 3 days in combination with a single exposure of ether vapor was highly suppressive in 16 of 20 mice (80%). Again, three consecutive metoclopramide (30 μg/g bw) in combination with a single injection of pentobarbital (50 μg/g bw) completely inhibited the pituitary bleeding in 39 out of 39 mice (100%). The combined pretreatment of a single high dose of metoclopramide (60 μg/g bw) and pentobarbital (50 μg/g bw) also resulted in the complete suppression of pituitary hemorrhage in 11 out of 11 mice (100%) (Table 7). Both a histamine receptor antagonist and a serotonin synthesis inhibitor had no effects on the bleeding.

Neither stimulative nor inhibitory effects on pituitary hemorrhage were observed in agents of all adrenergic receptor agonists except for norepinephrine and epinephrine, and antagonists (Tables 6 and 7).

DISCUSSION

The present study demonstrated new data concerning experimental manipulations and pharmacological agents

which stimulated or suppressed the occurrence of pituitary hemorrhage induced by the ip injection of a 35% glucose solution in mice.

Physiological study

An efficacious dose of a 35% glucose solution to induce pituitary bleeding is in a narrow range of a sublethal dose, and it depends on age of animals. In our previous studies, a 9% NaCl solution was given to induce pituitary hemorrhage in mice and a sufficient dose for the induction was 0.03 ml/g bw [13]. When a 8.5% NaCl solution of the same dose was used, no pituitary bleeding had been observed in ddY mice [22, 23]. In the present study, a dose of 0.02 ml/g bw of a 35% glucose solution was ineffective to induce pituitary bleeding in young male mice. In old mice, however, a low dose (0.02 ml/g bw) of a 35% glucose solution was sufficient to produce pituitary hemorrhage. This is probably due to either age-associated attenuation in the physiological tolerance to acute dehydration caused by the ip injection of a hypertonic solution or an absolute increase in the volume of the glucose solution injected in old mice (ca. 40–45 g). Therefore, male mice at 5–6 weeks of age and weighing about 30–35 g were used in the present experiments.

Water deprivation for 3 days significantly elicited the occurrence of this pituitary hemorrhage. Gradual dehydration by water deprivation and a subsequent acute dehydration by the ip injection of a hypertonic solution (a sub-threshold dose) could exert their effects on the pituitary bleeding additively in mice. Under this pretreatment of water deprivation, the pituitary seemed to be highly susceptible to subsequent changes in plasma osmolality. Water deprivation-associated rise in osmolality [1], a large increase in the anterior pituitary dopamine content [6] and also an increase in dopamine receptors of human pituitary adenomas [14] are assumed to be involved in the possible mechanism of this pituitary hemorrhage.

In contrast, the decline in the incidence of pituitary hemorrhage in nursing dams may relate to attenuation of inhibitory control by dopamine over prolactin secretion during nursing behavior [6, 17]. Thus, it is likely that a reduced dopamine activity could arrest this pituitary bleeding in mice. Hematocrit values were not different between the control dams and nursing dams each other, so alterations in the condition of body fluid might be ruled out in this case.

An acute rise in osmolality seems to be one of factors necessary to produce pituitary hemorrhage, because pituitary hemorrhage occurred after the injection of a 35% glucose solution in the present study. A gradual increase in osmolality (mOsm/l) by water deprivation did not induce pituitary bleeding [1]. The ip injection of hypertonic saline is assumed to increase serum viscosity by rapid transport of water from the blood into the peritoneal cavity, resulting in high osmotic pressure of the blood [23]. Heavy congestion of hypertonic solution revealed by electron microscopy [13] might reflect the increased serum viscosity.

Pharmacological study

Enhancement of pituitary hemorrhage was obtained by the pretreatment of norepinephrine, epinephrine, bromocriptine and thiamazole in mice given an insufficient low dose (0.02 ml/g bw) of a 35% glucose solution. At present, it is hard to deduce a common action of these agents to explain a possible mechanism of this pituitary bleeding. However, vascular excitatory action of these agents may be partly involved in the pituitary hemorrhage. Epinephrine and norepinephrine are potent vasopressor drugs [10, 24], and epinephrine has long been known to accelerate blood coagulation in animals and man [9]. Both α- and β-adrenoreceptor agonists and antagonists had neither stimulative nor inhibitory effects on pituitary hemorrhage, although epinephrine and norepinephrine enhanced a hypertonic solution-induced-hemorrhage. Association of bundles of unmyelinated nerve fibers with blood vessels in the anterior pituitary was often observed, and these nerve fibers are assumed to be not vasomotor nerves in rats [16]. Epinephrine and norepinephrine may act at vascular systems other than the pituitary portal one.

Furthermore, bromocriptine is a potent dopaminergic agonist at D_2 receptors [18]. Bromocriptine is well known to regress the bulk of tumors such as prolactin- and growth hormone- secreting adenomas. Pituitary apoplexy occurring in the course of chronic bromocriptine therapy has been reported in man [25], suggesting that bromocriptine suppression of the growth of pituitary adenomas resulted from a necrosis of the tumor tissue followed by hemorrhage into adenomas. Although pituitary apoplexy has not been described as a complication of bromocriptine therapy in man, the pretreatment of bromocriptine has induced significant enhancement of the pituitary hemorrhage in mice. Bromocriptine must have acted as a dopaminergic agonist at the pituitary level.

The use of thiamazole, an anti-thyroid gland drug, was based on the previous observation that thyroidectomy in rats usually resulted in apparent congestion of the anterior pituitary (unpublished data). These actions of thiamazole may be indirect ones, because TRH raised blood pressure in hypothyroidal animals [11]. A significant increase in portal plasma flow (140%) in hypothyroid rats rendered by propylthiouracil has been demonstrated [7]. Although it is uncertain that responses of TRH secretion and of blood flow could occur immediately after the administration of thiamazole, either direct or indirect actions of thiamazole might be involved in the mechanism of this pituitary bleeding.

Pituitary apoplexy has been documented in patients given a triple bolus test of TRH, LRH and insulin [5]. Thus, various hormones and agents are known to cause incidental pituitary apoplexy in man. In the present study, catecholamines, dopamine agonists and anti-thyroidal drugs were shown to enhance the incidence of experimental pituitary hemorrhage through an unestablished mechanism(s) in mice.

On the contrary, agents that arrested pituitary hemorrhage were haloperidol, metoclopramide, ether vapor and

pentobarbital. Haloperidol, metoclopramide and sulpiride were used as dopaminergic blockers [8, 19]. There is a good contrasting relation between effects of dopamine receptor agonists as an enhancer of the pituitary hemorrhage in mice and those of dopamine receptor antagonists as a suppressor. The rates of suppression of pituitary hemorrhage with haloperidol, sulpride and metoclopramide were, however, rather low (20%), although pharmacologically over-doses were used. In this connection, the present study indicated that the combined pretreatment of dopamine antagonists and anesthetics resulted in complete suppression of the pituitary hemorrhage in some cases.

Anesthetics such as pentobarbital and ether vapor alone showed a highly suppressive effect on the bleeding by 80.0% and 47.1%, respectively. In our previous experiments, neither intestinal peristalsis nor pituitary bleeding occurred although a rather excess volume of a hypertonic solution was infused into the opened peritoneal cavity of mice after laparotomy under ether anesthesia (unpublished data). Thus, inhibition of pituitary bleeding by anesthetics may be related to deterioration of the intestinal peristalsis, but at least to the reported action of brain ischemia by barbital [20, 21]. When peristalsis was enfeebled by anesthetics, the intestines could not respond normally to hypertonic solutions and the incidence of pituitary hemorrhage would be lowered.

If the site of action of dopamine antagonists and anesthetics is different, combined treatment with dopamine antagonists and anesthetics would give additive or synergistic effects on pituitary hemorrhage. As speculated, combination of pentobarbital (50 μg/g bw) and metoclopramide (60 μg/g bw) resulted in complete suppression of this pituitary bleeding. However, ED_{50} should be matched between two agents of pentobarbital and metoclopramide. The present study is the first report on experimental manipulations as to stimulation and inhibition of the hypertonic solution-induced pituitary hemorrhage in mice. The exact mechanism of this bleeding remains to be disclosed.

As to the organ specificity of this pituitary hemorrhage, the specific vascular architecture of the anterior pituitary may be concerned. The capacity of the venous connections draining the adenohypophysis to the cavernous sinus appeared small when compared to that of the long portal vessels supplying the adenohypophysis [3, 4]. Thus, it is supposed that venous hyperemia would easily take place in the anterior pituitary when the inflow of the blood into the gland is larger than the outflow in mice given the ip injection of a hypertonic solution.

No enhancement of the pituitary bleeding was observed by the pretreatment of vasopressin, adrenocorticotropin, 5-hydroxytryptophan and 5-hydroxytryptamine, respectively, probably due to lack of interaction of these agents to the sinusoidal capillaries of the anterior pituitary in mice.

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